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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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Additional inventors are being named on the 0 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Organic/Inorganic Interface Adhesion, Based on Self-Assembled, Mesoporous Oxide Films

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☑ Drawing(s) *Number of Sheets* 6 ☐ Other (specify)

☐ Application Date Sheet. See 37 CFR 1.76

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☑ Applicant claims small entity status. See 37 CFR 1.27.

☑ A check or money order is enclosed to cover the filing fees.

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Respectfully submitted,

SIGNATURE

Date 2/18/04

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Docket Number: S03-018/PROV

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FEE TRANSMITTAL for FY 2004

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80

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2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X		=
Independent Claims		- 3** =		X		=
Multiple Dependent						=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
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Other fee (specify) _____

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SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Dr. Steven Stupp	*Registration No. (Attorney/Agent)*	54,475	*Telephone*	650-424-0100
Signature				*Date*	2/18/04

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Provisional US Patent Application

of

Dimitrios Pantelidis and John C. Bravman

for

Organic/Inorganic Interface Adhesion, Based on Self-Assembled, Mesoporous Oxide Films

Field of the Invention

This invention is related to the field of improved adhesion at interfaces through the use of mesoporous films. More particularly, it is related to the improved adhesion of organic polymer layers on inorganic substrates through the use of self-assembled mesoporous films. It is also related to the incorporation of therapeutic drugs or other bioactive molecules in the pore network of self-assembled mesoporous coatings deposited on the surface of medical devices and the controlled release of such molecules following device implantation in patients for therapeutic purposes.

Background

The mechanical reliability of interfaces formed between organic polymer layers and inorganic surfaces is of critical importance for a variety of microelectronics, aerospace and biomedical applications. However, interfaces between such dissimilar materials pose certain challenges for adhesion. Most inorganic solids are usually covered with a hydrophilic native surface oxide that is characterized by the presence of surface hydroxyl groups (M–OH, where M represents an atom of the inorganic material, such as silicon or aluminum). At ambient conditions, at least a monolayer of adsorbed water molecules covers the surface, forming hydrogen bonds with these hydroxyl groups. Therefore, hydrophobic organic polymers do not spontaneously wet and adhere to the surface. Furthermore, even if polymer/surface bonds (including covalent bonds) are formed under dry conditions, these bonds are susceptible to hydrolysis upon exposure to water. This effect is particularly important in applications where devices or components containing organic/inorganic interfaces must operate in aqueous, corrosive environments such as the human circulatory system.

Two different approaches are traditionally followed to reinforce organic/inorganic interfaces. The first is chemical modification of the inorganic surface via amphiphilic silane coupling agents that improve polymer wetting, bonding and interface resistance to water. The second is the introduction of controlled roughness or porosity on the inorganic surface that induces polymer mechanical interlocking.

Silane coupling agents are materials that exhibit both hydrophilic and hydrophobic behavior, and are thus termed amphiphilic. Their molecules have the general structure $Y(CH_2)_nSiX_3$, $[Y(CH_2)_n]_2SiX_2$ or $[Y(CH_2)_n]_3SiX_3$, comprising a carbon chain (typically $n<20$), a hydrolysable group (X) forming hydrophilic silanols (Si–OH) in solution and a hydrophobic group (Y) selected for chemical affinity with the polymer of interest.

When a hydrophilic inorganic surface is treated with a silane solution, the hydrophilic silanols undergo condensation reactions with surface hydroxyl groups forming oxane bonds with the surface (Si–O–M). Similar to polymer/substrate bonds, silane/substrate oxane bonds are susceptible to hydrolysis but at rates several orders of magnitude lower. Siloxane bonds (Si–O–Si) also form by condensation of silanols belonging to adjacent coupling agent molecules. This results in a network of cross-linked molecules and the surface is usually covered with a several monolayer-thick film.

On the other hand, the hydrophobic silane groups improve the polymer wetting of the treated surface by lowering the surface energy. Partially cross-linked coupling agent oligomers can diffuse in the polymer matrix and improve the adhesion by mechanical interlocking. If the reactivity of the hydrophobic end group is tailored to match that of the polymer, the interface can be further strengthened by co-polymerization and covalent silane/polymer bonding.

While silane groups have been used to improve adhesion between organic/inorganic interfaces and reduce hydrolysis, there remains a need for further improvements especially in aqueous, corrosive environments.

Attempts to engineer the interface morphology to improve adhesion typically focus on introducing roughness or porosity to the inorganic surface. The rough or porous surface can be created either by selective material removal from an initially flat surface or by deposition of a porous film.

Polymer wetting of the rough or porous surface results in increased contact area, so that more bonds can be established between the two materials. Furthermore, the adhesion can be improved by a change in the failure mode. A perfectly flat organic/inorganic interface will generally fail adhesively, by crack propagation along the weakest-link path in the microstructure. In contrast, rough morphology results in mechanical interlocking of the polymer and pore impregnation creates a composite phase in the interface region. Crack propagation will now likely occur by both interface adhesive and polymer cohesive failure. The latter is associated with crazing, a process in which polymer fibrils bridge the debond opening and connect the two mating fracture surfaces behind the crack tip. The fibrils undergo plastic deformation before rupture, dissipating energy and increasing the macroscopic interface fracture resistance.

Although a rich variety of methods are available for creating rough or porous surfaces, such as metal anodization, grit-blasting, sintered beads, plasma-sprayed powder, porous fiber metal pads and nanoporous spin-on-glass formulations, these methods are either complex and expensive or offer limited control over the structural features of the porous surface. Clearly, properties such as pore size, alignment and interconnectivity determine the accessibility of the porous network to the interdigitating polymer, the extent of interlocking that can be achieved and the mechanical reliability of the composite phase formed upon polymer impregnation. Control over these properties is of critical importance and remains a challenge.

Mesoporous films provide an attractive option for imparting porosity on an inorganic surface with excellent control over the structural properties. The term mesoporous refers to the conventional classification of porous materials based on the actual size of the pores. Materials with pore size in the range of 2 nm and below are termed microporous, those in the range 2-50 nm mesoporous and those with pore size above 50 nm macroporous. The mesoporous regime is particularly interesting because it matches the diameter of the molecular chains of many engineering polymer, as well as that of proteins, pharmaceuticals and other biological molecules.

Fabrication of highly-ordered mesoporous ceramics via methods that employed a self-assembling surfactant template was first reported in the early 1990s. Since then, important progress has been made in the template-assisted preparation of mesoporous

solids of a wide compositional range on a variety of substrates, including highly-ordered mesoporous SiO_2 films with hexagonal and cubic symmetry. Furthermore, the fabrication method has been expanded to include self-assembling amphiphilic triblock copolymers as the structure-directing template. These materials are particularly attractive because they are commercially available at low cost and biodegradable, allowing for cost-effective and environmentally benign manufacturing.

In general, the structure-directing agent and a soluble inorganic precursor are initially mixed in solvent, and the substrate surface is spin-, dip- or spray-coated with the solution. Upon solvent evaporation, the template molecules spontaneously organize into a highly ordered, liquid-crystalline, mesoscopic array that directs the co-assembly of the inorganic species around it. Because of this cooperative self-assembly process, the symmetry and periodicity of the template determines the structural properties of the final mesoporous material, such as pore size, shape, alignment and interconnectivity. As already mentioned, a variety of architectures can be obtained, including structures of hexagonal and cubic symmetry, by appropriate selection of materials, solution concentration and pH, and processing.

Because of their unique structural properties and ease of processing, mesoporous films have been widely recognized as important candidates for applications as varied as catalyst supports, membranes and selective adsorbents; optical waveguides, sensors and photovoltaic cells; and low-*k* dieletrics. To date, however, mesoporous films have not been used to engineer improved adhesion of organic polymers to inorganic surfaces.

Annapragada (US Pat No 6,465,365) teaches the use of nanoporous silica films to improve the adhesion of an inorganic film and an inorganic substrate. Rutherford et al. (US Pat No 6,318,124) teaches the use of nanoporous silica on an inorganic substrate with an organic polymer coating. Rutherford etal., however, addresses the problem of producing a low-k dielectric. As a consequence, the pores in the nanoporous silica in Rutherford et al. need to remain open in contrast with the present invention, where the organic polymer is interdigitated through the pores in the mesoporous film. Furthermore, the organic polymer coating in Rutherford et al. is used to promote film cohesion, i.e., the mechanical strength of the nanoporous film, not the adhesion of the organic polymer to the inorganic substrate. In addition, the silane used in Rutherford et al. also has a

different function. It is a precursor that it polymerized to produce the organic polymer coating; it is not used as a pore modifier to improve the interdigitation and adhesion of the organic polymer.

In light of this background, there remains a need in the art for an improved adhesion between organic and inorganic interfaces especially in aqueous, corrosive environments.

Summary

The objects and advantages of the present invention are secured by an apparatus and method for improved adhesion of organic polymers and inorganic substrates through the use of mesoporous films. In the preferred embodiment, the mesoporous films have cubic symmetry. In the present invention, a two-layer interface of an organic polymer deposited on an inorganic substrate is replaced with a three-layer sutructure, namely one comprising the organic polymer of interest on top, a hybrid organic/inorganic mesoporous film in the middle (one resulting from interdigitation through the thickness of the mesoporous film with the organic polymer of interest), and the inorganic substrate at the bottom.

In the present invention, the adhesion is improved by interdigitation and mechanical interlocking of the organic polymers in the interconnected, periodic pores of the mesoporous film. The adhesion between organic polymers and inorganic substrates may be further improved by chemical bonding through the optional inclusion of silane groups or other surface modifiers on the surface of the pores in the mesoporous film. The silane groups lower the surface energy, encouraging the organic polymers to flow through the pores in the mesoporous film and couple to them, and thereby enhancing the interdigitation and, thus, the adhesion.

The present invention has numerous applications including total hip arthroplasty and expandable endovascular stents for treatment of coronary artery disease

Brief Description of the Figures

Fig. 1 is a drawing with a 3-dimensional mesoscopic template with cubic symmetry.

Fig. 2 is a drawing of a cubic mesoporous SiO_2 film on a substrate surface.

Fig. 3 a top-view scanning electron microscope (SEM) image of a cubic SiO_2 mesoporous film surface.

Fig. 4 a cross-sectional SEM image of the cubic SiO_2 mesoporous film on the surface of an inorganic substrate.

Fig. 5 Small angle x-ray spectrum of a mesoporous film

Fig. 6 is a graph of the effect of the mesoporous film on the critical adhesion G_c as a function of polymer curing time.

Detailed Description

Mesoporous films exhibit a remarkably ordered, open, surface-accessible pore channel network, continuously interconnected throughout the entire film volume. This property makes the films ideal for the class of applications related to this invention, because an organic polymer deposited on the top surface can access and penetrate the porous film through its thickness, creating a tough nanocomposite phase that extends all the way to the underlying inorganic substrate surface.

Fig. 1 shows the triblock copolymer template chains, self-assembled into a highly-ordered, 3-dimensional scaffold of cubic symmetry. The inorganic phase, not shown here, fills up the space around the channels defined by the template. The channels have excellent size uniformity, with diameters that are in the mesoscopic regime (5-30 nm) and can be precisely controlled via hydrothermal treatment or the addition of hydrophobic swelling agents in the initial solution. In a subsequent step, thermal treatment or room temperature exposure to a UV/ozone environment removes the template and induces cross-linking of the surrounding inorganic phase into a mechanically robust network. Thus, the final material is the negative of what is shown in Fig. 1, with the template channels being replaced by blank space and becoming the pores.

Figs. 2 illustrates the tri-layer structure **10** of the present invention. A mesoporous film **110** is deposited on an inorganic substrate **100**. An organic polymer **120** is interdigitated through the mesoporous film **110**. In a typical mesoporous film **110** in the present invention, the average diameter of the pores **130** is between 5-10 nm and the surface density of access points to the pore network from the film top is on the order of

$10^{12}/cm^2$. A top-view scanning electron microscope (SEM) image of the pores **130** in the mesoporous film **110** is shown in Fig. 3 and a cross-sectional SEM image of the tri-layer structure **10** is shown in Fig. 4. Returning to Fig. 2, the organic polymer **120** is interdigitated through the mesoporous film **110** thickness all the way to the underlying inorganic substrate **100**, as illustrated by the hatched region in the pores **130**.

The mesoporous SiO_2 films **110** are produced using the following recipe. First, the substrate surface is cleaned of any undesired contamination and prepared as appropriate for the specific application. Then, the template-assisted, cubic mesoporous film **110** is deposited on the inorganic substrate **100**. This is done by first mixing the templating agent, the inorganic precursor and any other necessary ingredients in a liquid solution as specified in detail in this application. The templating agent can be any amphiphilic inorganic, organic or hybrid organic-inorganic material comprising at least one hydrophilic and one hydrophobic part, which is capable of self-assembling in aqueous or non-aqueous solutions and of directing or assisting the co-assembly of the inorganic precursor (see below). Examples of such materials are ionic or non-ionic surfactants, sulfates, sulfonates, phosphates, carboxylic acids, alkylammonium salts, gemini surfactants, cetylethylpiperidinium salts, dialkyldimethylammonium, primary amines, poly(oxyethylene) oxides, octaethylene glycol monodecyl ether, octaethylene glycol monohexadecyl ether and block copolymers. Preferably, the templating agent is an amphiphilic triblock co-polymer containing at least one hydrophilic and one hydrophobic block component, with the general structure of -(hydrophilic block-hydrophobic block-hydrophilic block)-, where the hydrophilic block can be polyethylene oxide and the hydrophobic block can be polyalkylene oxides, such as polypropylene oxide and polybutylene oxide, or it can be based on polyisoprene, polybutadiene, polydimethylsiloxane or any other hydrophobic component. Inorganic precursors may include any sol-gel precursor including, but not limited to, any member of the group tetraalkylorthosilicate, such as tetraethylorthosilicate, tetramethylorthosilicate, any member of the groups alkyl-trialkoxysilane, dialkyl-dialkoxysilane, alkylene-trialkoxysilane, any member of the group tetraalkylorthotitanate such as titanium methoxide, titanium ethoxide, titanium butoxide, and titanium isopropoxide, any member of the groups alkyl-trialkoxytitanium, dialkyl-dialkoxytitanium, alkylene-

trialkoxytitanium, or any other similar sol-gel precursor where the metal atom is Zr, Al, Nb, Ta, W, Sn, Hf, Zn, Vn, Mn or any combination thereof. The chemical composition of the cubic mesoporous film **110** is determined by the inorganic precursor of choice, and can include metal oxides such as SiO_2, TiO_2, ZrO_2, Nb_2O_5, Ta_2O_5, Al_2O_3, WO_3, SnO_2, HfO_2, ZnO, Vn_2O_5, Vn_3O_9, Vn_4O_{12}, MnO and $Mn_8O_{26}(OH)_2$, and mixed oxides such as $SiAlO_{3.5}$, $SiAlO_{5.5}$, $SiTiO_4$, Al_2TiO_5, $ZrTiO_4$ and ZrW_2O_8. Organic groups may also be incorporated in the mesoporous film, for example via use of an alkyl-trialkoxysilane or alkyl-trialkoxytitanium sol-gel precursor as listed above, or any other appropriate precursor. Such organic groups may be incorporated to optimize the mesoporous film flexibility and overall mechanical properties as well as its surface properties, or its biocompatibility for biomedical applications.

Deposition of the solution on the surface of the inorganic substrate **100**, which can be flat or of complex shape and arbitrary curvature, can be performed by spin-, spray- or dip-coating. The final thickness of the mesoporous film **110** can be optimized by diluting the solution, or varying the spin-, dip- or spray-coating rates, or any combination of the above, as described in detail in the examples in this application. Following coating, the inorganic substrate **100** is subjected to drying so as to evaporate or otherwise remove the solvent. This can be done via a variety of processes such as drying at room temperature or at an elevated temperature, or subjecting the inorganic substrate **100** to mechanical rotation or otherwise accelerating the inorganic substrate **100** to drive off the solvent via centrifugal or inertial forces, respectively, or a combination of the above. Following that, and after the self-assembly process is complete, the template can be removed by thermal treatment or exposure to UV irradiation/ozone atmosphere.

Optionally, the surface of the inorganic substrate **100** and the walls of the pores **130** of the mesoporous film **110** can be chemically modified after removal of the template using a silane coupling agent, or any other surface modifier that is most appropriate for the specific polymer of the specific application. The coupling agent or surface modifier can be deposited from the gas phase or the liquid phase.

The polymer of interest is then deposited on top of the cubic mesoporous film **110** via spin-coating of a precursor formulation and induced to enter the pores **130** of the mesoporous film **110**, via capillary action or thermal treatment, preferably penetrating the

mesoporous film **110** in its entire thickness. This is followed by cross-linking of the organic polymer **120** via thermal curing, photocontrolled reaction or any processing steps required to obtain the desired final organic polymer **120** material from the precursor formulation that was used for deposition and penetration of the pores **130**. Optionally, this step can be accompanied or followed by formation of covalent or other chemical bonds between the organic polymer **120** and the modified walls of the pores **130** and the surface of the inorganic substrate **100** so as to further improve the adhesion.

EXAMPLES:

The organic polymer **120**/native-SiO_2/silicon inorganic substrate **100** interface was investigated. This interface was reinforced with a cubic mesoporous SiO_2 film **110**. The organic polymer **120** employed was a glassy, thermoset material derived from the polymerization of divinylsiloxane bis-benzocyclobutene and used in various microelectronics applications. In the rest of this document, this material will be referred to as BCB.

Polished 3" test grade silicon <100> inorganic substrate **100** wafers were purchased from Silicon Quest International. Vinyltriethoxysilane [CH_2=$CHSi(OCH_2CH_3)_3$], tetraethylorthosilicate [TEOS, $Si(OCH_2CH_3)_4$, 98%], triethylamine [$N(-CH_2CH_3)_3$], ethanol (CH_3CH_2OH, dehydrated, 200 proof) and triblock copolymer Pluronic F_{127} {$H(OCH_2CH_2-)_{106}[-OCH(CH_3)CH_2-]_{70}(-OCH_2CH_2-)_{106}OH$} were purchased from Gelest, Arcos Organics, Fisher Scientific, Gold Shield Chemical, and Sigma Chemical respectively, and were used as received, without further purification. Hydrochloric acid (HCl) of 0.02 M molar concentration (0.02 moles/lt) was prepared by mixing appropriate amounts of de-ionized water (DI H_2O) and concentrated hydrochloric acid (36% wt, 10 M) purchased from J. T. Baker. The BCB precursor was Dow Chemical Cyclotene 3022-35 {divinylsiloxane-bis-benzocyclobutene, $[C_2H_2C_6H_4CH=CHSi(CH_3)_2-]_2O$}.

The list of ingredients used to prepare the surfactant/silica solution, along with respective amount mixed, molecular weight, number of moles and relative molar concentration in the solution are shown in Table I.

Table I. Composition of solution

Ingredient	Amount Mixed	Mol. Weight (g/mol)	Moles	Molar Ratio
Tetraethoxyorthosilicate	5.2 g	208	0.025	1
Pluronic F_{127}	2.5 g	13,388	1.85×10^{-4}	7.4×10^{-3}
De-ionized Water	2 g	18	0.125	10
0.02 M Hydrochloric Acid	2.5 g	–	5×10^{-5}	0.002
Ethanol	60 ml	46	1.055	42

The mixing recipe used was:

- 5.2 g of TEOS, 2 g of de-ionized water (DI-H_2O), 2.5 g of 0.02 M HCl and 30 ml of ethanol were mixed in a glass flask and heated at 60 ^{0}C for 15 min, while stirred with a magnetic stirrer.
- 2.5 g of Pluronic F_{127} and 30 ml of ethanol were mixed in a separate glass beaker and heated at 60 °C for 15 min, then removed from hot plate and stirred with magnetic stirrer for 15 min.
- The above two solutions were then mixed together in the flask and heated at 60 ^{0}C for 15 min, while stirred with the magnetic stirrer.

Once mixed, the solution is stable and can be stored at room temperature and used repeatedly to prepare batches of samples for up to one month. Further dilution with pure ethanol allows preparation of films with variable thickness.

A combination of solution dilution and deposition via variable spin-coat rate has allowed us to obtain the cubic SiO_2 mesoporous film **110** on flat surface of the silicon inorganic substrate **100** wafer with film thickness in the range of 10-150 nm. Similar variation in film thickness can be obtained by combination of solution dilution and variable dip-coat rate.

Dilution was performed by mixing a measured amount of the original solution with a corresponding amount of pure ethanol. In the final solution, the concentration of all the ingredients is lowered by the same factor. Since the self-assembly mechanism relies on solvent evaporation, the mechanism is not affected by the dilution process, as long as the relative molar concentration (molar ratio) of the solutes is not altered. Generally, lower absolute concentration and higher spin-coat rates (or lower absolute concentration and lower dip-coat rates) result in lower film thickness, as characterized by ellipsometry and summarized in Table II. In the preferred embodiment, we deposited the 25 nm-thick cubic SiO_2 mesoporous film **110** by using the appropriate combination of dilution and spin-coat rate, as described in Table II.

Table II. Thickness of cubic mesoporous SiO_2 films 110 as a function of dilution and spin-coat rate.

Vol. diluted solution / Vol. original solution	Spin-coat Rate (krpm)	Thickness (nm)
1	4.5	147±3
2	9	55.5±1.5
4	9	24±0.5
10	9	9.5±0.5

In one example, (100) silicon inorganic substrate **100** wafers were cleaned for 10 min in a "Piranha" solution (1:3 H_2O_2:H_2SO_4), then rinsed and spin-dried. Then 3 ml of 4:1 diluted solution was applied on the cleaned wafer surface using plastic disposable pipettes and deposited via spin-coating at a spin-rate of 9,000 rpm. The template was removed immediately after spin-coating by thermal treatment in ambient air. The temperature was incrementally raised by 1 °C/min until the target temperature of 400 °C was reached, then the samples were allowed to cool off.

Next, the porous surface was treated with a 5% wt solution of vinyltriethoxysilane coupling agent in ethanol with trace amounts of triethylamine added to catalyze siloxane bond formation with the walls of the pores **130**. The vinyl functionality was selected to

allow co-polymerization with BCB. Ethanol, coupling agent and catalyst were first mixed in ambient air, then the wafer was immersed and the container heated at 60 °C. Wafers were removed after 30 min, cleaned for 5 min in ethanol under ultrasonic vibration and blow-dried using a nitrogen gun. Any excess solvent that may remain in the pores **130** after blow-drying can be removed by evaporation, at ambient temperature or at an appropriate elevated temperature.

After silanation the organic polymer **120** precursor was deposited via spin-coating. 3 ml of the precursor solution was applied on the cleaned wafer surface using plastic disposable pipettes and spun at 2,500 rpm. According to the manufacturer, this results in an approximately 5 μm-thick film, as confirmed by ellipsometry measurements. Two identically prepared, BCB-coated wafers were then placed face-to-face so as to form a silicon inorganic substrate **120**/native-SiO_2/SiO_2 mesoporous film **110**/BCB organic polymer **120**/ SiO_2 mesoporous film **110**/native-SiO_2/silicon inorganic substrate **100** sandwich structure. The sandwich structures were then cured in a nitrogen atmosphere and under approximately 25 kPa of compressive stress provided by the weight of a 3"-diameter W cylinder put on top of them. The temperature profile was:

- Ramp for 1 hr to 150 °C.
- Soak for 5 hrs at 150 °C to allow precursor flow through the pores **130**.
- Ramp for 1 hr to 250 °C (cross-linking temperature).
- Soak for various time intervals (30-120 min) at 250 °C and let cool off.

As discussed below, varying the soak time at 250 °C allows the effect of organic polymer **120** plasticity on interface adhesion to be varied.

Upon removal from the nitrogen oven, the sandwich structures are diced to create test specimens that are tested for interface fracture energy G_c using the 4-Point Bend experimental set-up. The theoretical background and the specifics of this technique have been described in detail in R.H. Dauskardt, M. Lane, Q. Ma, and N. Krishna, "Adhesion and debonding of multi-layer thin film structures," *Engineering Fracture Mechanics* **61** (1), 141-62 (1998). Each pair of sandwich-bonded 3" wafers provide approximately 20

fracture specimens after dicing, and the reported adhesion strength is the average of all G_c values measured for specimens originating from the sandwich.

Control silicon inorganic substrate **100**/native-SiO_2/BCB organic polymer **120**/native-SiO_2/silicon inorganic substrate **100** samples were also prepared and tested. The native oxide surface of these wafers was cleaned and silanated and the BCB precursor was deposited and cured following the processing steps described above. In the following discussion of the characterization, the control samples will be referred to as flat-SiO_2/BCB, whereas the reinforced interface will be referred to as mesoporous-SiO_2/BCB.

Each mesoporous film **110** was characterized immediately after template removal. Film thickness was measured with a Gaertner Scientific ellipsometer equipped with a He-Ne Laser (λ=632.8 nm) at an incident angle of 70° relative to the surface normal. The pore **130** channel structure (shown in Fig. 3) was imaged using a Hitachi Scanning Electron Microscope (SEM).The mesoscopic symmetry of the films was characterized via Small-Angle X-Ray Scattering (SAXS) diffraction experiments using a Philips X'Pert diffractometer with a Cu K_a source. Fig. 5 shows a SAXS spectrum obtained from the SiO_2 mesoporous film **110** after template removal. Because of the mesoscopic scale symmetry (d-spacings in the 5-10 nm range), the peaks occurred at very small angles ($2\theta < 5°$) and are superimposed on the reflectivity signal of the substrate. Indexing of the observed peaks is consistent with three-dimensional cubic symmetry (the space group has been identified as $Im\bar{3}m$).

Interface adhesion can best be quantified in terms of the macroscopic interface fracture energy G_c, also called critical adhesion, measured in J/m^2 and expressed as a sum of two terms:

$$G_c = G_o + G_{pl} \qquad (1)$$

G_o includes the energy required for bond rupturing and atomic-scale plasticity at the crack tip. G_{pl} accounts for energy dissipation processes occurring at an extended zone surrounding the debond area. When ductile polymer layers are present, the predominant energy absorbing mechanism is plastic deformation and the dissipation zone term is

substantially higher than the near-tip one. For the experimental method used in this study, G_c can be obtained from the applied strain energy release rate required for interface debonding.

In order to study the effect of the BCB layer plasticity on adhesion, samples have been cured for variable time intervals in the range of 30-120 min at the cross-linking temperature of 250 °C. The manufacturer recommends curing the material for 60 min. Longer soak times drive the polymer chain cross-linking reaction towards completion, suppressing the ability for plastic deformation. Therefore, interface adhesion is expected to decrease with increasing soak time.

Critical adhesion values for the mesoporous SiO_2-reinforced interface are plotted as a function of polymer curing time in Fig. 6, and compared to corresponding critical adhesion values for the flat-SiO_2/BCB control interface. In all cases, the porous interface significantly outperforms the control. For the 60 min cure recommended by the manufacturer, the strengthening effect is higher than 50%. As expected, the effect scales with curing time. These results, which are summarized in Table III, indicate that the present invention significantly reinforces the adhesion of organic/inorganic interfaces.

Table III. Experimental G_c values as a function of polymer curing time for mesoporous-SiO_2/BCB and flat-SiO_2/BCB (control) interfaces.

	Mesoporous-SiO_2/BCB		**Flat-SiO_2/BCB**	
Curing time (min)	**G_c (J/m^2)**	**Std (J/m^2)**	**G_c (J/m^2)**	**Std (J/m^2)**
30	97	11	58.5	9
60	66.5	13	41	5
120	43.5	7.5	33	9.5

There are numerous applications of the present invention. One is total hip arthroplasty. Failure of the polymethylmethacrylate (PMMA) cement/metal interface of the femoral component has been recognized as a major cause of aseptic loosening of cemented hip implants. Experimental and numerical studies have concluded that interface debonding can significantly increase the stresses in the surrounding cement mantle, leading to PMMA cracking and overall implant failure.

Several approaches have been considered to improve the reliability of the polymer/metal interface. One of the most promising has been precoating of the implant with a 30-50 μm-thick PMMA layer, accomplished at elevated temperatures where the lower viscosity of the polymer is expected to allow better wetting of the metal surface. This is often combined with implant surfaces roughened via a variety of methods (grit-blast finish, glass-bead finish, belt finish). The imparted morphology is designed to promote polymer interlocking and average roughness size is generally in the 0.5-15 μm range. Furthermore, it has also been demonstrated that surface treatment with silane coupling agents significantly improves the precoat/implant interface adhesive strength and its resistance to environmentally assisted fatigue.

However, a significant trade-off inherent in the use of rough implant surfaces has been reported. Roughness increases the polymer/metal adhesive strength but smoother implants are less abrasive and generate less debris in the event of partial interface debonding. Moreover, there appears to be a correlation between rougher implants and increased occurrence of bone tissue damage (osteolysis), patient pain and more immediate need for surgical revision.

The present invention is ideal for secure femoral component fixation, without sacrificing the documented advantages of polished implants. The mesoporous film **110** material can be selected according to the implant material of choice. SiO_2 films can be deposited on Co-Cr-Mo, while TiO_2 films would likely be ideal on Ti6-Al4-V components. In combination with the appropriate silane adhesion promoter, excellent bonding between the implant and the precoated PMMA material can be established. The superiority of this approach for adhesion over the traditional roughness imparting techniques has been discussed in the present invention. Additionally, the roughness of the surface of the mesoporous film **110** is several orders of magnitude smaller. This characteristic should be beneficial in preventing debris generation and bone loss.

As a final note, the SiO_2 mesoporous film **110** has already been discussed in the literature in the context of medical implant coatings. The SiO_2 mesoporous film **110** deposited on Ti6-Al4-V alloy substrates and exposed to simulated body fluid have been shown to induce precipitation of hydroxyapatite crystals. However, because of the pore size range, it appears unlikely that the mesoporous film **110** would prove useful in

cementless joint replacement applications, as implied in these studies. Pores **130** with sizes in the range of 50-100 μm have been reported as the necessary minimum to allow bone tissue in-growth throughout a porous coating. In contrast, as discussed in the present invention, the mesoporous regime is ideal for accommodating polymer molecular chains.

Another application of the present invention is in expandable endovascular stents for treatment of coronary artery disease. This has been one of the most important advances in interventional cardiology since the introduction of Percutaneous Transluminal Coronary Angioplasty (PCTA). However, in-stent restenosis due to neointimal hyperplasia after treatment remains a major complication. Drug-eluting stents have generated tremendous excitement as a potential solution, and an extensive research and clinical effort is under way to identify the ideal combination of stent design, surface coating matrix and locally delivered pharmaceutical compound. A wide variety of polymer coatings have been considered as the drug host matrix. In most cases, the coating is designed to act as a porous, sponge-like reservoir, capable of absorbing sufficient amounts of the drug and releasing it over a period of time after device implantation. Biocompatibility, complexity and cost of the deposition method, drug uptake capacity and release kinetics are all critical factors related to the coating material selection. In addition, adhesion of the coating to the stent before and after expansion is a critical factor for device functionality and long-term reliability.

Recently, mesoporous silica powders of hexagonal symmetry, in which the pores are non-interconnected, aligned cylindrical channels (mesoporous materials exhibiting this structure are often referred to as MCM-41) were shown to be capable of absorbing and releasing bioactive molecules, such as the anti-inflammatory drug ibuprofen. Although these studies highlight the feasibility of employing mesoporous materials in drug-delivery systems, it is clear that supported, continuous coatings, rather than powders, are required in the context of drug-eluting stent applications.

The oxide mesoporous film **110** and the methods for deposition thereof described in detail in this invention offer two improvements for the stent application. The first is an improved adhesion/reliability of the organic polymer **120** drug-carrying coating on the stent surface. The second is the use of the mesoporous film **110** as the drug-carrier itself,

replacing the organic polymer **120** coatings that are used in stents currently on the market. In the first case, the oxide mesoporous film **110** in this invention is an efficient and versatile strategy for successfully anchoring any organic polymer **120** coating to the underlying stent scaffold, which functions as the inorganic substrate **100**. The processes discussed in this invention allow for deposition of the mesoporous film **110** that is continuous and that can uniformly cover a surface of the inorganic substrate **100** of arbitrary complexity and curvature. In the second case, as illustrated in Fig. 1, the process of the present invention result in the mesoporous film **110** with a remarkably ordered pore channel network, continuously interconnected throughout the entire film volume and accessible via a dense array of surface entry points. This property is critical, because it also allows loading the mesoporous film **110** with a drug after the mesoporous film **110** has been deposited on the stent.

Sawitowski et al., in "Implant with Cavities Containing Therapeutic Agents," in WO 00/25841. 2000: Germany, have developed and patented a competing technology based on nanoporous alumina (aluminum oxide, Al_2O_3) coatings deposited via electrochemical methods. The technology has been commercialized by AlCove Surfaces GmbH and a stent platform featuring this coating loaded with the drug tacrolimus (JoStent, manufactured by Jomed) is currently in clinical trials (the PRESENT study, led by Grube et al.). The mesoporous film **110** described in this present invention provides a drug-delivery vehicle that is significantly more versatile and reliable than the AlCove nanoporous alumina, while exploiting a drastically simpler, less expensive and more environmentally benign fabrication method.

The process for producing the mesoporous film **110** for this application is similar to that already described in this invention. First, the stent surface, which is the inorganic substrate **100,** is cleaned of any undesired contamination and prepared for film deposition. Then, a cubic mesoporous film **110** is deposited on the stent. This is done by first mixing the templating agent, the sol-gel inorganic precursor and any other necessary ingredients in a solution, then coating the stent surface with the solution and evaporating or otherwise removing the solvent. After the self-assembly process is complete, the template is removed by thermal treatment or exposure to UV irradiation/ozone atmosphere. The chemical composition of the thus-obtained mesoporous coating **110** is

determined by the choice of sol-gel precursor, so as to optimize the biocompatibility, affinity with the stent substrate, coating flexibility and overall mechanical properties, the uptake capacity and release kinetics of the therapeutic agent of interest.

Optionally, the stent surface and the walls of the pores **130** of the mesoporous film **110** can be chemically modified after template removal, using a silane coupling agent, or any other surface modifier that is most appropriate for improving the biocompatibility of the coating, the uptake capacity and release kinetics of the therapeutic agent of interest. The coupling agent or surface modifier can be deposited from the gas phase or the liquid phase.

Following that, or at any later time, including shortly before device implantation, the therapeutic agent is incorporated in the pores **130** of the mesoporous film **110**. After this step is complete, the device is ready for implantation.

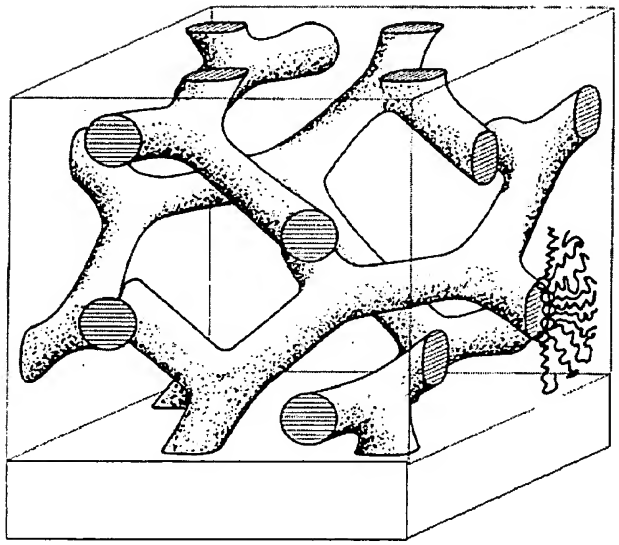

Fig. 1

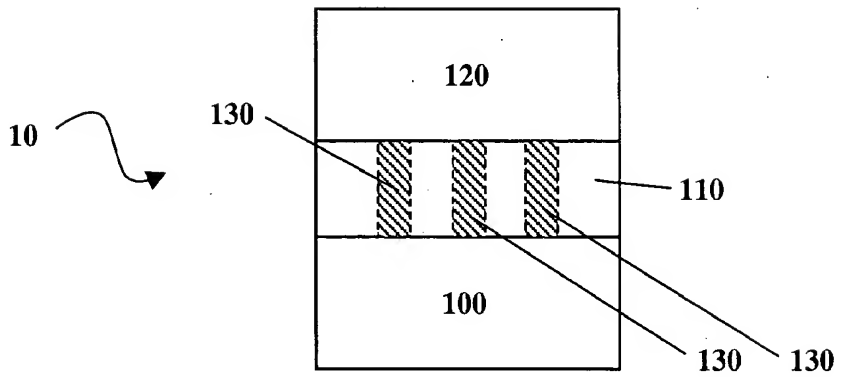

Fig. 2

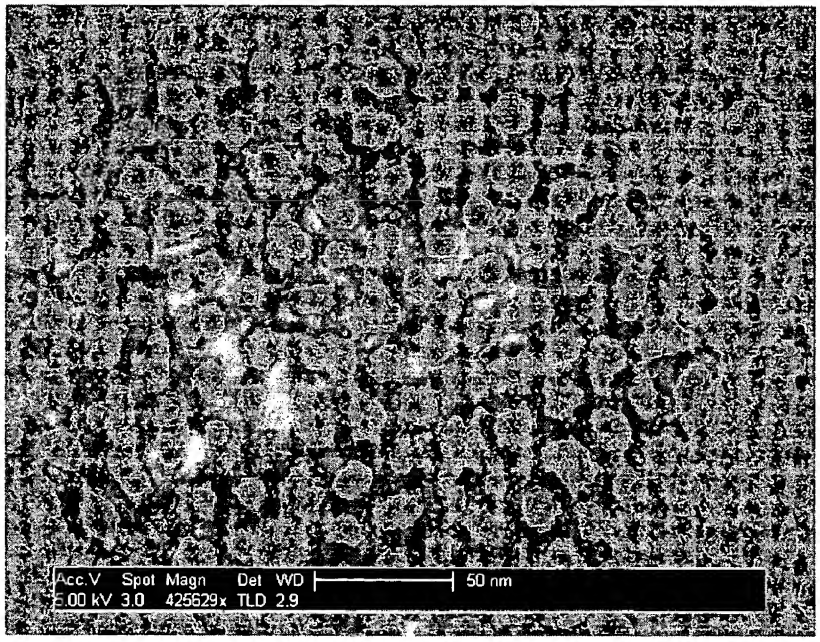

Fig. 3

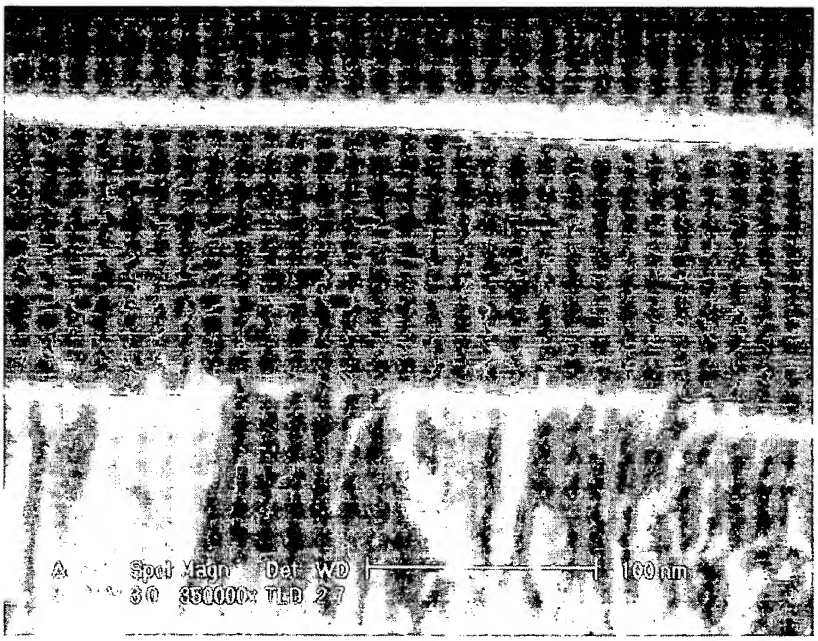

Fig. 4

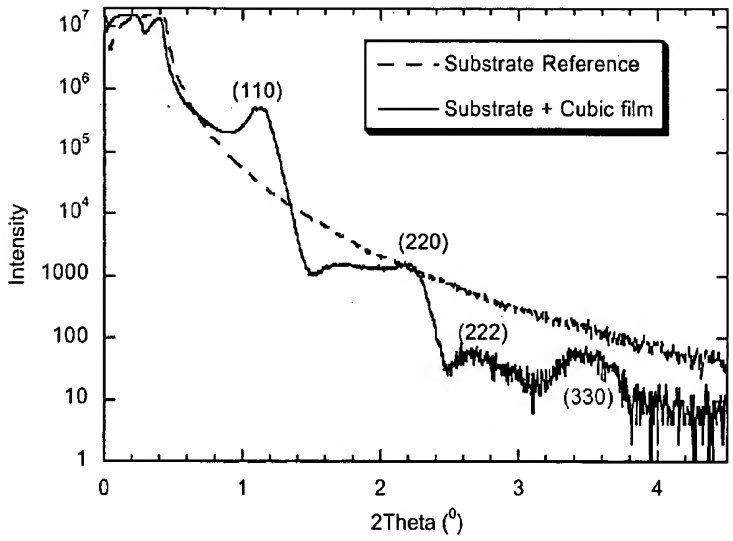
Substrate Reference
Substrate + Cubic film
(110)
(220)
(222)
(330)
Intensity
2Theta (0)
10^7
10^6
10^5
10^4
1000
100
10
1
0
1
2
3
4

Fig. 5

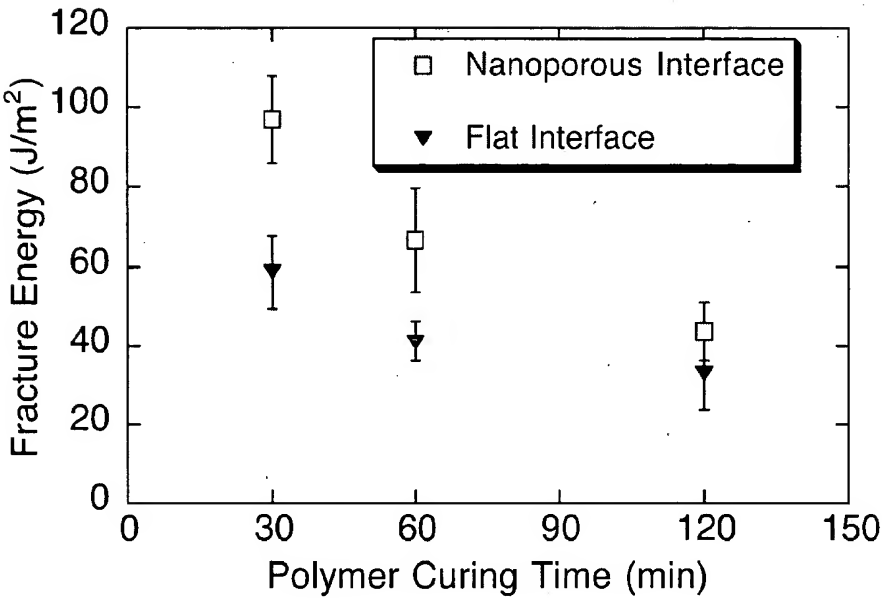
120
100
80
60
40
20
0
Fracture Energy (J/m^2)
0
30
60
90
120
150
Polymer Curing Time (min)
Nanoporous Interface
Flat Interface

Fig. 6